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RESEARCH PAPER

NanoRiskCat: a conceptual tool for categorization and communication of exposure potentials and hazards of nanomaterials in consumer products

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Abstract The literature on nano(eco)toxicology is growing rapidly and has become increasingly difficult to interpret. We have developed a systematic tool called NanoRiskCat that can support companies and regulators in their first-tier assessment and communication on what they know about the hazard and exposure potential of consumer products containing engineered nanomaterials. The final outcome of NanoRiskCat is communicated in the form of a short-title describing the intended use and five colored dots. The first three dots refer to the qualitative exposure potential for professional end-users, consumers and the environment, whereas the last two refers to the hazard potential for humans and the environment. Each dot can be assigned one of four different colors, i.e. red, yellow, green, and gray indicating high, medium, low, and unknown, respectively. In this paper, we first introduce the criteria used to evaluate the exposure potential and the human and environmental hazards of specific uses of the nanoproduct. We then apply NanoRiskCat to eight different nanoproducts. The human and environmental exposure potential was found to be high (i.e., red) for many of the products due to direct application on skin and subsequent environmental release. In the NanoRiskCat evaluation, many of the nanomaterials achieve a red human and environmental hazard profile as there is compelling in vivo evidence to associate them with irreversible effects, e.g., carcinogenicity, respiratory, and cardiovascular effects, etc., in laboratory animals. A significant strength of NanoRiskCat is that it can be used even in cases where lack of data is prominent.

Keywords NanoRiskCat · Decision-support tool · Health · Environment · Risk assessment · Exposure potential

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Introduction

Manufactured nanomaterials are used in a rapidly increasing number of products available to industries and private consumers and the diversity of commercialized nanomaterials and products is immense. More and more evidence has emerged in the scientific literature that some nanomaterials might have hazardous properties (for a comprehensive review, see Stone et al. 2010; Mikkelsen et al. 2011; SCHER, SCENIHR, and SCCS 2013). However, it is a great challenge to clearly extract and communicate the essence of exposure and hazard information efficiently. Traditional risk assessment

procedures of chemicals have numerous limitations and barriers that need to be overcome before they can be applied effectively to nanomaterials (Paik et al. 2008; Hansen 2009). A number of alternative or supplementary concepts, approaches and frameworks have been proposed with the intention to estimate and control to risks of nanomaterials. For nanomaterials used in the laboratory Paik et al. (2008) and Zaik et al. (2009) have developed the "Control Banding Nanotool" whereas more generic tools such as the "Swiss precautionary matrix", Stoffenmanager Nano, the ANSES tool and CB Tool NanoSafer have been developed by Höck et al. (2010), Van Duuren-Stuurman et al. (2012), ANSES (2010), and Jensen et al. (2011), respectively. A few concepts and tools originally developed for traditional chemicals have also been revised in regard to nanomaterials such as "comprehensive environmental assessment" (Davis 2007) and "multicriteria decision analysis" (Linkov et al. 2007; Tervonen et al. 2009; Hristozov et al. 2012, 2013). When it comes to nanomaterials, several of these tools have profound advantages as compared to traditional risk assessment, but even for these "science-based" alternative approaches the requested information or data input (e.g., surface reactivity) requires methods that have yet to be clearly specified or harmonized (Grieger et al. 2012; Hansen et al. 2011). Furthermore, most of the existing tools are intended for evaluation of pure nanomaterials in workplace scenarios. Only a few of the tools include the possibility for assessment of products and articles, consumers and the environment. As there is already a general lack of information and data on nanomaterials, uncertainty and knowledge gaps are prone to increase as the material passes into the environment or down-stream to the industrial user, importer, vendor, consumer, and end of life. Previously, there has not been a systematic approach for nanomaterial manufacturers, producers, and regulators to assess the immediate hazard and exposure potentials on a given nanomaterial-based product in a regulatory perspective and pass this knowledge downstream.

To address this issue, we have developed a nanomaterial risk categorization concept, called NanoRiskCat (NRC) that can be used to support companies and regulators in identifying, assessing, ranking, and communicating what they know about the potential exposure and hazards of a given nanomaterial used in consumer products (Hansen et al. 2011).

In its simplest form the conclusion from a NanoRiskCat evaluation is communicated in the form of a short-title describing the intended use of the nanomaterial (e.g., TiO_2 in sunscreen) and a five colored dots, three for exposure and two for hazard (Fig. 1). The first three dots always indicate the exposure potential of professional end-users, consumers, and the environment and the last two dots refer to the hazard potential for humans and the environment. The dots can be colored red, yellow, green, and gray indicating high, medium, low, and unknown, exposure potential or hazard, respectively.

In the following, we will first introduce the criteria used in NanoRiskCat to evaluate the exposure potential and the human and environmental hazards of specific uses of nanomaterials as well as the procedure used to assign colors. According to the on-line PEN inventory of nanotechnology-based consumer products (Project on Emerging Nanotechnologies 2013), the most commonly used nanomaterials are: silver, carbon (including C_{60} and carbon nanotubes), titanium, silicon/silica, zinc, and gold. Therefore, we present the application of NanoRiskCat on eight different nanoproducts—one product for each of the seven most used nanomaterials in consumer products as well as one product for which

Fig. 1 Example of a NanoRiskCat evaluation on exposure and hazard potential for a given nanoproduct. The first three *colored dots* always refer to the exposure potential during intended use for professional end-users, consumers and the environment, respectively. The last *two dots* refer to the apparent hazard potential for humans and the environment, respectively. Each *dot* can be assigned one of four different colors and the colors *red*, *yellow*, *green*, and *gray* indicate high, medium, low, and unknown, respectively

the identity is unknown. Such examples of products with unknown nanomaterial ingredients are highly realistic, as a previous analysis has shown that the nanomaterial was not reported in almost 60 % of the products in PEN inventory (Hansen et al. 2008). In order to show the versatility of the proposed framework, the eight different products vary not only in regard to the used nanomaterial, but also with regard to which product category (e.g., cosmetics, sunscreen, and sports equipment) they fall under and with regard to how much information is made available publicly by the producers.

Procedure for the NanoRiskCat evaluation

Step 1: Short titles for use scenario(s) and nanomaterial identification

In order to clearly communicate the scope and boundaries to the NanoRiskCat evaluation, the evaluated nanoproduct must be clearly specified in a short title, defining the specific nanomaterial(s) used in the product, if known, and the intended use.

Step 2: Assessment of the exposure potential

As a second step, NanoRiskCat requires an evaluation of the potential exposure to professional end-users, consumers, and the environment for the specific nanomaterial in the evaluated nanoproduct.

When reporting on the exposure potential for a chemical substance to professional end-users for regulatory purposes, a substantial amount of information is needed including, e.g., the physical state and vapor pressure of the substance (ECHA 2010). For nanomaterials and nanoproducts such information is still very rarely available. Dustiness data on nanomaterial powders start to appear in the scientific literature (Schneider and Jensen 2008; Tsai et al. 2009; Jensen et al. 2009; Dahmann and Monz 2011; Burdett et al. 2013), but is still rarely given in technical data sheets or in the material safety data-sheet. Moreover, very little is known about the release and/or exposure levels during professional end-use and regular consumer uses. Even less is known on the environmental release during use and discard of the products. Nevertheless, the number of process-related nanomaterial emission studies is now rapidly growing and data have emerged on, e.g., spraying (e.g., Nørgaard et al. 2009; Hagendorfer et al. 2010), mechanical abrasion and cutting (e.g., Koponen et al. 2011; Wohlleben et al. 2011; Golanski et al. 2012), and use degradation (e.g., Kaegi et al. 2008, 2010; Lorenz et al. 2012; Wohlleben et al. 2013) of nanoproducts. If such data are available on the specific products or product groups subject to the NanoRiskCat evaluation, they naturally must be taken into consideration. However, this appears rarely the case. Most producers/distributors do not even provide information about the identity and content of the nanomaterials in their product, which is highly problematic.

In NanoRiskCat a simple framework inspired by Hansen et al. (2007, 2008) is used to sort the consumer product into four different exposure categories:

1. High exposure potential.
2. Medium exposure potential.
3. Low exposure potential.
4. Unknown due to lack of information.

The categorization is partly based on the location of the nanomaterial in the products, i.e., is the nanomaterial located in the bulk, on the surface, liquid or airborne? (see Hansen et al. (2007) for guidance on how to determine the location of the nanomaterial) as well as a judgment of the potential for nanomaterial exposure based on the product use description. According to categorization in Hansen et al. (2008) and abovementioned release studies, exposure is certainly likely when the nanomaterials are not fixed or embedded in a solid and hence "High exposure potential" with red color code is given to products which contain ''nanoparticles suspended in liquids'' or result in ''airborne nanoparticles" during use. For ''surface-bound nanoparticles'', the exposure potential is assumed to be possible, Hence there is a "Medium exposure potential" and such products are assigned a yellow color code. It should be noted that if the product use description involves sanding the surface, the color code should be red due to risk of nanoparticle release (Koponen et al. 2011; Saber et al. 2012a; Wohlleben et al. 2011; Golanski et al. 2012). The reason is that release of nanoparticles from matrix cannot be excluded per default, especially from paints with low strength matrices, poor quality, high energy paint removal, or if subjected to weathering (Koponen et al. 2011; Saber et al. 2012a; Golanski et al. 2012). The actual consequence of this release is still uncertain

as current studies indicate that the toxicity of dusts generated by mechanical abrasion or sanding of nanocomposite materials is not increased as compared to that of nanoparticles-free paints (Saber et al. 2012a, b; Wohlleben et al. 2011). Finally, if the products contain "nanoparticles suspended in a solid", it is thought that there is a low or negligible exposure potential associated with their intended use. Hence such products should as a general rule be assigned a color code of green. Again, from the discussion above, if the use description involves mechanical modification by cutting, sanding or grinding, this color code should be red. As in the case of occupational exposure estimation of chemicals, personal protection equipment (PPE) is generally not considered in the first exposure estimation even when it might be used (ECHA 2010).

NanoRiskCat human hazard evaluation

Criteria used to assess the human hazard of a nanomaterial

The potential human health hazard of a given nanomaterial in a given nanoproduct is evaluated using a number of different criteria, which are evaluated sequentially. Depending on whether the criteria is or is not fulfilled a hazard color code is eventually assigned (see Fig. 2). The criteria or qualifiers to be considered are:

1. Does the *nanomaterial* classify as a High Aspect Ratio Nanoparticle (HARN)? In order to be classified as a so-called HARN the nanomaterials must have a high surface area and a length to diameter aspect ratio greater than 10 to 1. Furthermore, it is required that: (1) The diameter of the fibers must be thin enough pass ciliated airways; (2) the length must be long enough to initiate the onset of, e.g., frustrated phagocytosis and other inflammatory pathways; and (3) the nanomaterials must be biopersistent (Tran et al. 2008). As shown in Fig. 2, a HARN classification will lead to a red color coding.
2. Is the nanomaterial in *bulk form* known or suspected to cause serious detrimental effects according to Regulation (EC) No 1272/2008 also known as the CLP Legislation (ECHA 2013), i.e., does the bulk form have one or more "Level A CLP classifications"? (see Table 1). Level A CLP classifications include the most serious health outcomes where the material is either known or strongly suspected to cause severe and potentially irreversible harm. The use of CLP information insures that previous knowledge is considered and enables broader identification of potential hazards associated with the material than if nanomaterials were reviewed alone. This read-across approach is naturally assuming that nanomaterials will not be less hazardous than the *bulk form*.
3. Is the *bulk form* of the nanomaterial classified for other less severe adverse effects, which we have defined as "Level B CLP classifications" (see Table 1). The reason these adverse effects are considered less severe is that the effects are described as reversible in the CLP hazard categories.
4. Is the specific *nanomaterial* known to induce acute toxicity? Acute toxicity is defined as adverse effects in laboratory animals resulting from an oral or dermal administration of a single dose or multiple doses within 24 h to a nanomaterial or an inhalation exposure of 4 h (ECHA 2008, United Nations 2009). Adverse effects could be clinical signs of toxicity, abnormal body weight changes, and/or pathological changes in organs and tissues, which in some cases may be lethal. Local irritation or corrosion of the gastrointestinal tract, skin or respiratory tract following a single exposure are included here as well and the same goes for cellular level acute toxicity such as (i) general basal cytotoxicity (ii) selective cytotoxicity and (iii) cell-specific function toxicity (ECHA 2008). The cut-off values that we have chosen to determine the toxicity of a nanomaterial is similar to the acute toxicity hazard category 4 in CLP (Regulation (EC) No. 1272/2008). For oral and dermal acute toxicity estimates (based on LD50/LC50 when available), the acute toxicity cut-off has been chosen by us to be 2,000 mg/kg. For inhalation of dusts and mists (solid particles and liquid droplets) the acute toxicity estimate cut-off has been set to 5 mg/l.
5. Is there indications that the nanomaterial causes genotoxic, mutagenic, carcinogenic, respiratory, cardiovascular, neurotoxic, or reproductive effects in humans and/or laboratory animals or has organ-specific accumulation been documented? As shown in Stone et al. (2010), Hougaard et al. (2010),

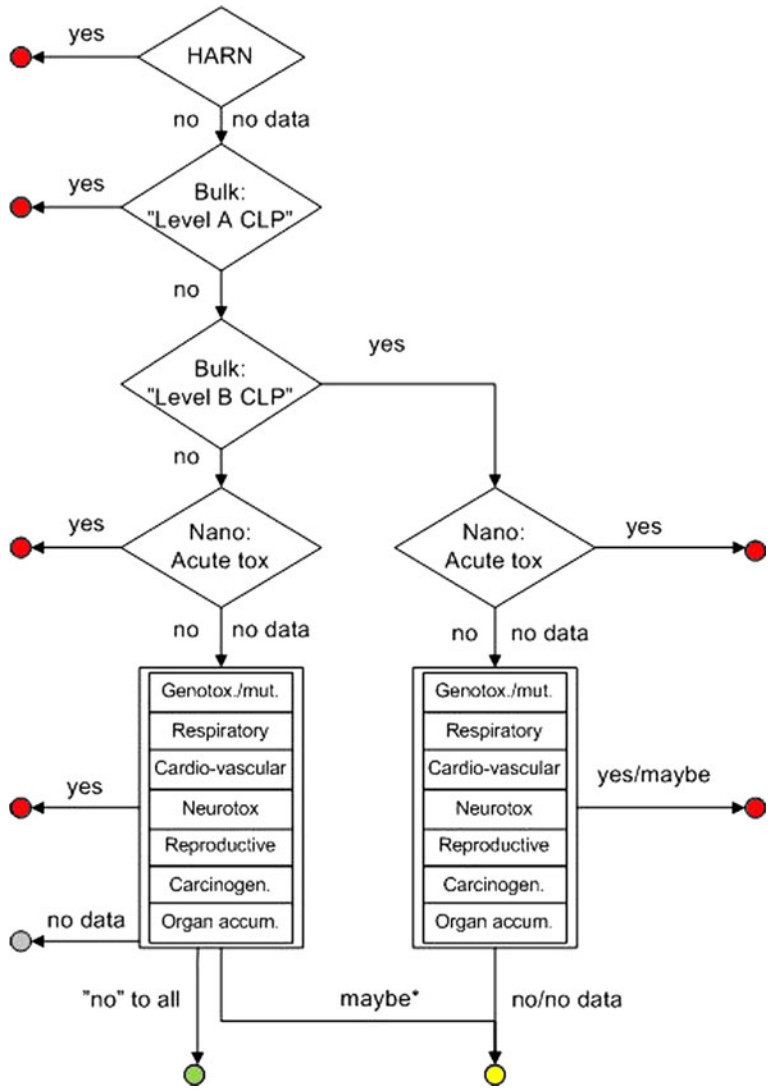

Fig. 2 Road-map for assigning a color code for the human hazard potential in NanoRiskCat. *Red*, *yellow*, and *green* indicate high, medium, and low indication of deleterious effect whereas *gray* indicates too limited data to make an assessment. *Asterisk* at least one "maybe" and the rest "no" or "no data"

Halappanavar et al. (2011), and Hansen et al. (2013a), there is compelling evidence that exposure to some nanomaterials may be associated with effects in one or more of these end-points. Due to their severity, a response significantly over background in any of these endpoints results in a "red" classification. For each of these endpoints, the user of NanoRiskCat has to review the literature and answer "yes", "no" or "maybe", e.g. yes, there are indications that the nanomaterials is genotoxic. Depending on whether a given nanomaterial has been associated with one or the other adverse effect and whether the answer(s) were yes, maybe, no or no data, the product is assigned a red, yellow, green or gray color code.

In case the answer is "yes" to any of these questions a red color code will be triggered. The red color code in Fig. 2 signifies that indications of adverse effects are high; the yellow signifies that indications of adverse effects are medium, and green that indications of adverse effects are low. Gray should be used if there are numerous data gaps and unknowns to warrant no conclusion to be made about the human hazards of the nanomaterial. If no CLP Level A classification is associated with the bulk material, the answer to this question would be "no", whereupon the next step would ensure in the flow diagram in Fig. 2. When the bulk form of the material has a classification that falls under "Level B CLP classification", the nanoform can no longer be classified as "green". In case a

Table 1 Level A and level B CLP classifications as irreversible and reversible effects by us, respectively

Level A CLP classifications as irreversible adverse effects	Level B CLP classifications as reversible effects
1. Acute toxicity category 1–4	1. Skin corrosion/irritation category 2
2. Germ cell mutagenicity category 1A, 1B, or 2	2. Specific target organ toxicity-single exposure category 3
3. Carcinogenicity category 1A, 1B, or 2	3. Serious eye damage/irritation category 2
4. Reproductive toxicity category 1 A, 1B, or 2	
5. Specific target organ toxicity—single exposure category 1 or 2	
6. Specific target organ toxicity—repeated exposure and category 1 or 2	
7. Aspiration toxicity category 1	
8. Skin corrosion/irritation category 1A, 1B, or 1C	
9. Serious eye damage/irritation category 1	
10. Respiratory and skin sensitization category 1	

nanomaterial does not have a bulk parent material (e.g., fullerene, nanotubes and organoclays) the answer to this question should be "no" by default. As a general rule, in cases where the bulk form has no CLP classification and the answer is "no" to each for these effects, this would result in a categorization as "green" whereas it would be "yellow" if the answer is "maybe" to at least one of the endpoints. On the other hand, if the bulk form of the nanomaterial has a Level B classification associated and there are indications of one or more adverse effects of the nanomaterial, this would lead to classification as "red". In case the bulk form has a Level B CLP classification and that there are no nanospecific adverse effects reported, this would lead to a classification as "yellow". No conclusion can be reached with regard to any of these effects, no categorization of the nanomaterial can be made and this would lead a classification as "gray".

It should be noted that NanoRiskCat is a tiered approach in the sense that once a color code has been triggered (e.g., bulk materials CLP classified as an acute toxic category 3 after oral exposure would trigger "red"), the nanomaterial cannot obtain a different color code (yellow, green, or gray) even though the oral LC50 might be > 300 mg/l but $\leq 2{,}000$ mg/kg bodyweight.

Interpreting the scientific evidence

Providing rigid rules for how to interpret data from scientific results is not feasible, but transparency is key and hence for each of these questions, reasoning should be provided with proper referencing to the scientific and/or non-scientific literature and an answer to each of the questions should be provided in form of either: yes, maybe, no, or no information. The answer "yes" implies that there is data giving cause to substantial concern that the nanomaterial in question may cause ir-/reversible effects (e.g., carcinogenicity) or that the nanomaterial holds a given property (e.g., persistency). "Maybe" indicates that data is not conclusive but gives cause to some concern, whereas "no" indicates that there is conclusive evidence that the nanomaterial does not cause adverse ir-/reversible effects and/or hold the properties in question. "No data", indicates that no or very limited and insufficient data is available for hazard evaluation.

In case of conflicting evidence from epidemiological and/or in vivo studies, the answer to Question 5 could still be "yes" if there are one or more reasonable explanations for why one of the studies did or did not observe an adverse effect. The answer could similarly be "no" if there are one or more reasonable explanations (e.g., confounders) for why a study did observe an adverse effect while another did not. Finally, the answer would be "maybe" in cases where there is conflicting evidence and no reasonable explanations for why results differ. In regard to in vitro testing, it has been shown that these studies may not always accurately predict potential hazards of nanomaterials in more complex biological environments (CCA 2008) and hence, indications of one or more adverse effects should be used either to discuss mechanisms of toxicity or in conjunction with other lines of evidence. In case no other lines of evidence are available, results stemming from in vitro studies can only be used to answer "maybe", as positive or negative indications of effects have only in some cases found to be reliable from in vitro toxicological tests (Sayes et al., 2007; Han et al. 2013; Dobrovolskaia and McNeil 2013).

Justification categories associated with human health hazard classification as red, yellow, and gray

To help communicate the scientific reasoning behind assigning a human health hazard classification and why a given nanomaterial was assigned red, yellow, or gray, a NanoRiskCat Table of justification categories have been developed. The options listed in Table 2 are meant to justify primarily whether the conclusion has been reached based on classification of the bulk form of the materials and/or in vivo or in vitro data on the nanomaterial and in regard to what endpoint. Depending to the final classification in regard to human health, the user of NanoRiskCat has to select one or more of those sentences that best reflect the scientific basis for assigning the color code. A

NanoRiskCat environmental hazard evaluation

Similar to the human health hazard evaluation, a number of indicators/qualifiers should be considered when evaluating the environmental hazards of a given nanomaterial and its application and subsequently assigning a color code (see Fig. 3). The criteria or qualifiers to be considered are:

1. Is the nanomaterial in question reported to be hazardous to environmental species?
2. Is the nanomaterial in question persistent?
3. Is the nanomaterial in question bioaccumulative?
4. Could use of the nanomaterial in question lead to potentially irreversible harm to the environment (e.g. ecosystem effects)?
5. Is the nanomaterial in question readily dispersed?
6. Is the nanomaterial in question novel?

In order to evaluate whether the nanomaterial in question may be hazardous to environmental species, the user has to consider if the *bulk form* of a nanomaterial has a CLP classification. For the environmental hazard, we distinguish between Level A CLP classifications, i.e. Acute 1 or Chronic 1 and Chronic 2 and Level B CLP classifications, i.e. Chronic 3 or Chronic 4. In case the *bulk form* of the nanomaterial has a Level B classification, documented nano-specific effects have to be considered as well e.g. statistically significant effects of nanomaterial observed without EC50 or LC50 values being established or non standardized endpoints have been applied.

The user of NanoRiskCat also has to consider whether the nanomaterial is hazardous to environmental species, i.e., LC50 or EC50 < 10 mg/l or < 100 mg/l. LC50-values or EC50-values from tests of nanomaterial with base-set organisms below 10 mg/l will lead to a red color coding whereas reported values below 100 mg/l will either lead to a red color coding or a subsequent evaluation of persistency and bioaccumulation potential. Values below 10 mg/l will traditionally be referred to as either toxic (1–10 mg/l) or very toxic (<1 mg/l) to aquatic organisms (ECHA 2013). The reason for assigning a red color code directly to materials with LC50- or EC50-values below 10 mg/l is the presently ongoing discussion on which dose-metrics will be the best to use in nano-ecotoxicology.

Another set of questions is related to whether the nanomaterial is persistent or bioaccumulative. Here, a nanomaterial is considered to be persistent if freshwater tests reveal a degradation half-life greater than 40 days in accordance with the OECD test hierarchy for degradability (OECD 2011). The criterion for classifying a chemical as bioaccumulative according to the REACH guidance is that the bioconcentration expressed as a bioconcentration factor (BCF) exceeds the value of 500 (ECHA 2012). However, the validity of the concept BCF as a measure for bioaccumulation is challenged by the multiple uptake routes for nanomaterials (Hankin et al. 2011). The biomagnification factor (BMF) may better represent the risk for uptake and transfer through the food chain of nanoparticles and therefore the BMF is chosen as the criterion for bioaccumulation in NanoRiskCat. In the ECHA guidance a value of BMF > 1 is used to indicated that a compound is bioaccumulative, i.e., that the concentration of a substance in an organism at one trophic level is higher than the concentration at the preceding level. In NanoRiskCat a cut-off value of 0.1 is used on a precautionary basis acknowledging that (1) analytical techniques for quantification of nanomaterials in both environmental media and biological tissues are not yet fully developed, and (2) that accumulation of nanomaterials may not be defined by total body burden, but more likely by a differential uptake and perhaps translocation to specific organs.

As indicated in Fig. 3 considerations on the transport, ecosystem effects and novelty should be included

Table 2 Additional sentences to explain the color code for human health hazard (HH) in NanoRiskCat

Sentence no.	Color	Description
HH 1		Based evidence of HARN
HH 2		Based on bulk CLP classification 1-4 for acute toxicity
HH 3		Based on CLP classification 1 for skin corrosion/irritation, eye damage/irritation/ respiratory and skin sensitization
HH 4		Based on bulk CLP classification 1 or 2 germ cell mutagenicity/carcinogenicity, reproductive toxicity, specific target organ toxicity
HH 5		Based on bulk CLP classification 1 for aspiration toxicity
HH 6		Based on nano acute tox
HH 7		a. Based on in vivo evidence of an effect when testing the nanomaterial, i.e., one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation
		b. Based on in vivo evidence of a combination of two or more of the following, i.e., one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation
HH 8		a. Based on in vitro evidence of an effect when testing the nanomaterial, i.e., one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation
		b. Based on in vitro evidence of a combination of two or more of the following, i.e., one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation
HH 9		Based on bulk classified as a CLP category 2 regarding skin corrosion/irritation/serious eye damage/irritation as well as in vivo evidence of hazards from testing of the nanomaterial
HH 10		Based on bulk classified as a CLP category 3 regarding specific target organ toxicity—single exposure as well as in vivo evidence of hazards from testing of the nanomaterial
HH 11		Based on bulk classified as a CLP category 2 regarding skin corrosion/irritation/serious eye damage/irritation as well as in vitro evidence of hazards from testing of the nanomaterial
HH 12		Based on bulk classified as a CLP category 3 regarding specific target organ toxicity—single exposure as well as in vitro evidence of hazards from testing of the nanomaterial
HH 13		Based on in vivo evidence indicating at least one hazard from testing of the nanomaterial
HH 14		Based on in vitro evidence indicating at least one hazard from testing of the nanomaterial
HH 15		Based on bulk classified as a CLP category 2 regarding skin corrosion/irritation/serious eye damage/irritation as well as evidence of no hazards from testing of the nanomaterial
HH 16		Based on bulk classified as a CLP category 3 regarding specific target organ toxicity—single exposure as well as evidence of no hazards from testing of the nanomaterial
HH 17		Based on bulk classified as a CLP category 2 regarding skin corrosion/irritation/serious eye damage/irritation as well as not enough data on possible hazards from testing of the nanomaterial
HH 18		Based on bulk classified as a CLP category 3 regarding specific target organ toxicity—single exposure as well as not enough data on possible hazards from testing of the nanomaterial
HH 19		Based on not enough in vitro and/or in vivo data being available on hazards from testing of the nanomaterial
HH 20		Based on the identity of the nanomaterial not being disclosed or available, which hampers any human hazard evaluation

as the final step. Regarding that the term "novelty", the UK Royal Commission on Environmental Pollution (RCEP 2008) distinguishes between four types of novel materials: (1) New materials hitherto unused or rarely used on an industrial scale; (2) New forms of existing materials with characteristics that differ signicantly from familiar or naturally occurring forms, e.g., silver and gold; (3) New applications for existing materials or existing technological products formulated in a new way, e.g., cerium oxide used as a fuel additive; and (4) New pathways and destinations for familiar materials that may enter the environment in forms different from their manufacture and envisaged use.

The outcome of these considerations is a written evaluation aimed at answering "yes", "maybe", "no"

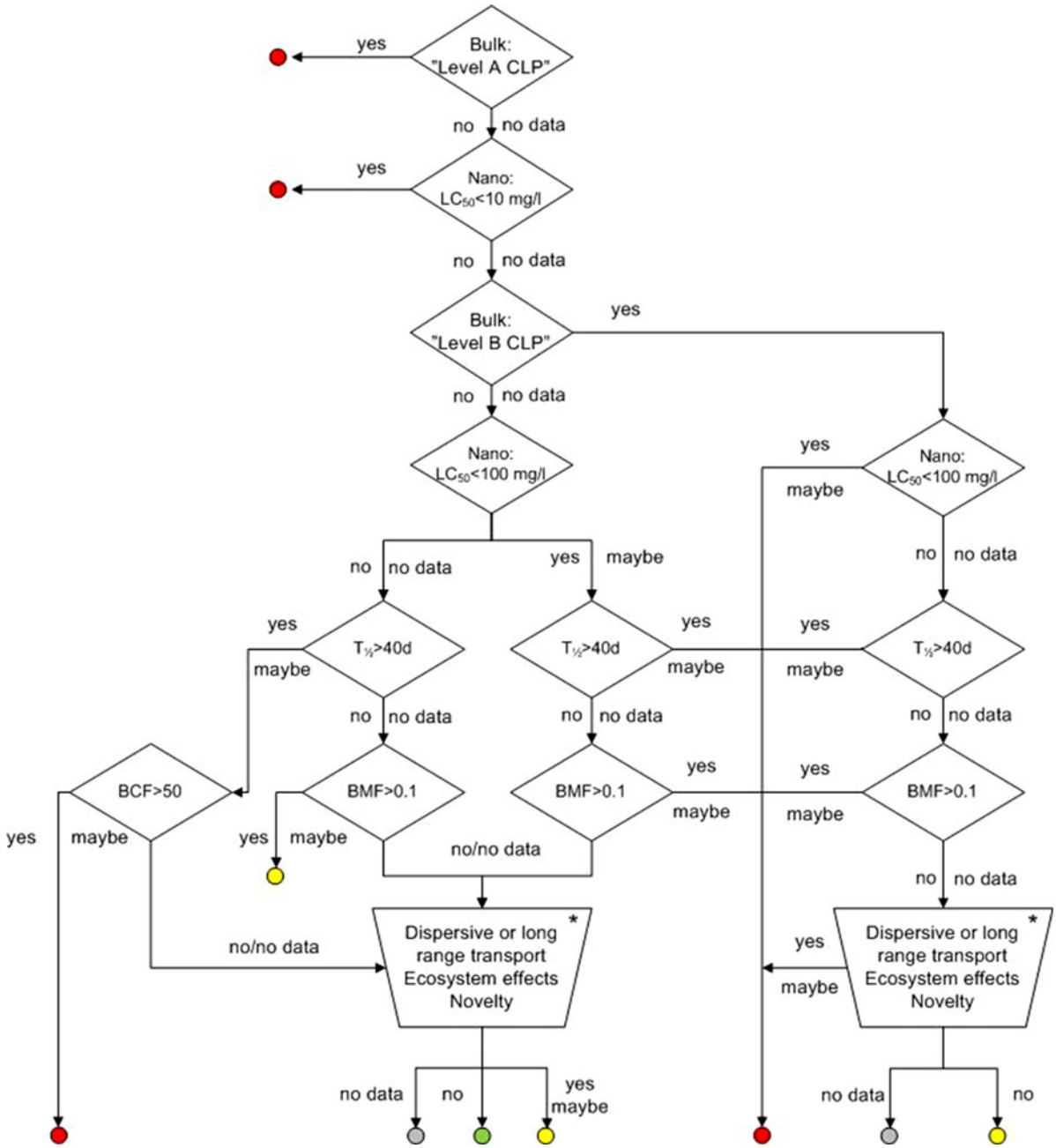

Fig. 3 Road-map for assigning an environmental hazard color code in NanoRiskCat. *Red*, *yellow*, and *green* indicate high, medium, and low indication of effect whereas *gray* indicates too limited data to make an assessment. Asterisk at least one ''maybe'' and the rest ''no'' or ''no data''

or "no data". The first question to be considered is: Is the nanomaterial dispersive? Although not something that is normally considered in the environmental hazard categorization, there is historical evidence that the mere fact that a substance or material is disperse in the environment is a good indicator of potential harm that has yet to become discovered (EEA 2001, Hansen et al. 2013b). In relation to this, data on the substance's

volatility, solubility, and mobility in (e.g., soil) would be of relevance for a "regular" organic chemical, but for nanomaterials, the volatility should be disregarded. The mobility in soil can only be evaluated on actual data measuring the distribution, since no estimation equations have been established for the time being. The second question to be considered is: could use of the nanomaterial in question lead to potentially irreversible harm to the environment (e.g., ecosystem effects)? In the case that a nanomaterial does not fulfill any of the criteria above, a series of broader questions and elements need to be taken in consideration. The first question is whether there are documented or potential ecosystem effects (e.g., through oxygen depletion, effects on nutrient balance, shifts in populations), but also effects on global scale like ozone depletion, or global warming potential. The final question to be considered is: are we dealing with a novel material? Although not something that is normally considered in the environmental hazard categorization, there is historical evidence that the mere fact that a substance or material is novel is a good indicator of potential harm that has yet to become discovered (EEA 2001). Novel would in this case be defined as materials that humans and environment have not previously been exposed to at any significant extent (RCEP 2008). As in the case of the human health hazard evaluation a number of standard sentences have been developed to help communicate the scientific reasoning behind assigning an environmental hazard classification and why a given nanomaterial was assigned red, yellow or gray (see Table 3).

Table 3 Additional sentences to explain the color code for environmental effects (EE) in NanoRiskCat

Sentence no.	Color	Description
EE 1		Based on bulk CLP classification of acute 1 or chronic 1 or chronic 2
EE 2		Based on nanospecific LC50 or EC50 <10 mg/l
EE 3		Based on possible or confirmative evidence of nanospecific LC50 or EC50 < 100 mg/l and *T*1/2 > 40 days
EE 4		Based on possible or confirmative evidence of nanospecific LC50 or EC50 < 100 mg/l and BMF > 0.1
EE 5		Based on evidence of *T*1/2 > 40 days and a BMF > 0.1
EE 6		a. Based on bulk CLP classification of Chronic 3 or Chronic 4 and nanospecific effects (LC50/EC50 < 100 mg/l or *T*1/2 > 40 days or BMF > 0.1) b. Based on bulk CLP classification of Chronic 3 or Chronic 4 and T1/2 > 40 days and a BMF > 0.1 c. Based on bulk CLP classification of Chronic 3 or Chronic 4 and an evaluation of dispersive or long range transport, ecosystem effects, and novelty
EE 8		Based on a BMF > 0.1
EE 9		Based on an evaluation of dispersive or long range transport, ecosystem effects, and novelty
EE 10		Based on bulk CLP classification of Chronic 3 or Chronic 4 and an evaluation of dispersive or long range transport, ecosystem effects, and novelty
EE 11		Based on an evaluation of dispersive or long range transport, ecosystem effects, and novelty
EE 12		Based on bulk CLP classification of Chronic 3 or Chronic 4 and an evaluation of dispersive or long range transport, ecosystem effects, and novelty
EE 13		Based on the identity of the nanomaterial not being disclosed or available, which hampers any environmental hazard evaluation

Eight examples of the application of NanoRiskCat

As mentioned in the introduction, we illustrate the applicability of NanoRiskCat by evaluation of eight different nanoproducts. Table 4 lists the products with a brief original product description from the vendors.

Development of eight short titles for use scenario(s) and nanomaterial identification

As noted earlier, it is important that the nanoproduct subject to the NanoRiskCat evaluation is clearly stated from the start. If enough information is made available on a given nanoproduct, the specific kind(s) of nanomaterial(s) and the intended use(s) of the product should be included in the form of a short title. Despite the aim to list clear information on the product name, the nanomaterial in the products and the intended

Table 4 Identity and some basic information about the eight products subject to the NanoCatRisk evalution

	Product name	Producer	What they claim	References
1	NANOVER™ Cleansing Soap	GNS Nanogist	"Since nanosilver is 50,000 times smaller than pore, even with small amount, it can be absorbed into between skin cells easily and quickly without any irritations. NANOVER™ Cleansing Soap excludes acnes and sebum, and also reduces pores, makes your skin clear. At the same time, through the elimination of skin remnants and waste matter, you can maintain your skin clear, light, and clean"	http://www.nanogist.com/English/products/soap.htm
2	XTC C60 5W40 synthetic special oil	Bardahl	"L'esclusiva FORMULA anti-attrito BARDAHL POLAR PLUS – FULLERENE per un triplo strato di protezione: un film lubrificante superficiale, una zona di MOLECOLE POLARI più le molecole di FULLERENE C60 come meccanismo di protezione finale. POLAR PLUS forma una pellicola molecolare lubrificante che, fissandosi chimicamente sul metallo, crea una barriera di protezione permanente riducendo drasticamente gli attriti su tutte le parti del motore." ("The exclusive anti-friction formula BARDAHL POLAR PLUS – FULLERENE for a triple protection layer: a lubricating surface film, a zone with POLAR MOLECULES plus FULLERENE C60 molecules as a mechanism for final protection. POLAR PLUS forms a molecular lubricating film which, by chemically sitting on the metal, creates a permanent protection barrier drastically reducing friction in all engine's parts. The FULLERENE C60 molecules works as micro-rolling bearing which, by sitting between metallic parts, further reduce friction and increase engine's power. The FULLERENE C60 added to the FORMULA POLAR PLUS ensure clearly better performance than traditional lubricants")	http://www.bardahl.it/lubrificanti_additivi/olio_motore/auto/lubrificante_motore_auto/lubrificanti_auto/xtc_c60_5w40.html
3	Babolat® NS™ Tour Tennis Racket	Babolat	"Carbon nanotubes are used to stiffen key areas of the racquet head and shaft." and that "100 times more rigid than steel [and 6 times lighter!], 10 times stiffer than conventional graphite. Carbon Nanotube™ is the ideal material. Extremely resistant and highly reactive, it provides power to the racquet through rigidity and playing sensations never experienced before"	http://www.tennisexpress.com/info/babolat-racquet-nanostrength-technology.cfm
4	Nano Titanium Satin Straightener	BaByliss Pro Stylist Tools	"Advanced floating Ceramic plates with Nano Titanium technology for smoother and faster results"	http://www.lookfantastic.com/babyliss-pro-nano-titanium-satin-straightener/10574165.html

Table 4 continued

	Product name	Producer	What they claim	References
5	Solar Rx SPF 30 + Nano-Zinc Oxide Sunblock	Keys Soap	"Nano-Zinc Oxide that is 10 times smaller than micronized zinc oxide provides more even coverage to reflect UVa and UVb radiation. The nanotechnology 25 nm particle is the perfect foundation for makeup. Add moisturizer and makeup to make you look great and be protected from damaging sun"	http://www.keys-soap.com/solarrx.html
6	NanoCotz™ Eco-Clean	Inspiraz	"NanoCotz™ Eco-Clean is an anti-static silicon dioxide coating that can be applied to nearly any hard surface. A single application converts most external surfaces to have the ease of maintenance by reducing static electricity. It has superior durability, which come into wide use for building and automotive exterior finishing. This protective coating is able to improve the exterior finishing durability. Reduce maintenance cost by prolonging the repainting period. For external facade walls of buildings, glass, exterior paintwork of automotive etc"	http://inspiraztech.en.gongchang.com/product/9044357
7	Nano Gold Energizing Cream	Chantecaille	"A powerful healing breakthrough, this extraordinary cream consistently replenishes skin's energy using nanotechnology to safely deliver the power of pure gold: in this revolutionary product, nanoparticles of 24-karat gold are bound to silk microfiber, a natural protein that is moisturizing, antioxidant and anti-inflammatory. Through nanotechnology, these elements reach the cellular level where they act as the ultimate healing and preserving force.Lactic acid and hydrolyzed wheat protein help skin better manage its resources, especially during times of stress, promoting energy"	http://www.saksfifthavenue.com/main/ProductDetail.jsp?FOLDER%3C%3Efolder_id=282574492711986&PRODUCT%3C%3Eprd_id=845524446197495&R=656509702909&P_name=Chantecaille&sid=120A0B312FA8&ASSORTMENT%3C%3East_id=1408474399545537&bmUID=1239646676269
8	Nano Synthetic Material Sealant	Percenta AG	"Our "Nanotechnology Synthetic Material Sealant" is a coating material on a nanotechnology level. It provides an easy to clean effect on synthetic surfaces (polyester, PMMA, PC). The applied sealant creates a thin, invisible film, which reduces the adhesion of dirt and other foreign matter. And water will be repelled"	http://en.percenta.com/nanotechnology-synthetic-materials-sealing.php

used, we observed some challenges for the eight selected products due to, sometimes very limited, information made available by the producers. Therefore, the most descriptive use sentences were:

1. Nanosilver used in NANOVER™ Cleansing Soap.
2. C_{60} used in Bardahl XTC C60 5W40 synthetic special oil.
3. Carbon nanotubes used to stiffen Babolat® NS™ Tour Tennis Racket.
4. TiO_2 used in BaByliss Pro Stylist Tools Nano Titanium Satin Straightener.

5. 25 nm Zinc Oxide nanoparticles used in UVa and UVb reflecting Solar Rx SPF 30 + Nano-Zinc Oxide Sunblock.
6. NanoCotz™ Eco-Clean protective silicon dioxide coating.
7. Gold used in Chantecaille Nano Gold Energizing Cream.
8. Unknown nanomaterial used in Percenta AG Nano Synthetic Material Sealant.

Exposure to professional end-users, consumers, and the environment

In the NanoRiskCat evaluation, the human exposure potential to nanomaterials in a given product is categorized based on the location of the nanomaterial in the product as well as general information about the use of the product. In the case of NANOVER™ Cleansing Soap produced by GNS Nanogist, the location of the nanosilver is assumed to be suspended in liquids, which leads to a red-color code for professional end-users and consumers. This corresponds well with the fact that the product is to be used directly on the skin. A possibility for environmental release and exposure is also to be expected especially during and after bathing and wash. The main outlets to the environment are expected to be directly into the water recipients and indirectly via the Sewage Treatment Plants into water recipient and soil.

In the case of XTC C_{60} 5W40 synthetic oil produced by Bardahl, the C_{60} is stated by the manufacturer to be suspended in the liquid lubricant, which leads to a red-color code for professional end-users and consumers. Direct human contact with C_{60} in the lubricant could occur to the skin, eyes, and potentially also to the airways by inhalation of droplets from splashing and spills during use. Indirect oral uptake of C_{60} oil could also easily occur through dermal transfer due to poor hand hygiene. Environmental release may occur during combustion, if the C_{60} oil is poorly combusted in the engine, use, leakages and oil-change. Unintended direct release may also occur if C_{60} adheres to metallic components of the car and therefore eventually will be incorporated in the end-of-life vehicle engine (Franco et al. 2007). Above considerations would lead to a red-color for this product in regard to the environmental exposure profile.

In the case of the Babolat® NS™ Tour Tennis Racket the carbon nanotubes are used to stiffen areas of racquet head and shaft. The nanomaterial is suspended in solids, which would lead to a green-color code for the professional end-user and consumers. The environmental exposure potential is assumed to be low during use of the racket given the nature of the product and the location of the nanomaterial. The fate of the carbon nanotubes in the waste-stream is poorly known at this point in time, but the racket is expected to enter the regular waste-streams after use and either end up in landfills or in an incinerator. Based on the above consideration, the environmental exposure potential of carbon nanotubes used in the tennis racquet is rather uncertain. Principally, incineration should result in combustion of the carbon nanotubes (CNTs) (green color), whereas landfill is expected to result in CNT release in the long-term (red color). In this case, we will categorize the environmental fate as unknown, which would lead to a gray-color code.

With regard to the Nano Titanium Satin Straightener the producer states that the ceramic plates have nano-titanium technology indicating that the nanomaterial is bound at the surface. Consequently, the exposure potential would be categorized as medium leading to a yellow-color code.

As in the case of NANOVER™ Cleansing Soap, the Solar Rx SPF 30+ Nano-Zinc Oxide Sunblock produced by Keys Soap and the Nano Gold Energizing Cream produced by Chantecaille fall into the category of products that have nanoparticles suspended in liquids. These occurrences lead to a red-color code for professional end-users and consumers. This corresponds well with the fact that the product is to be used directly on the skin. The likelihood of environmental exposure potential is also assumed to be high especially during and after bathing and wash. The main outlets to the environment are expected to be either directly into the water recipients and/or indirectly via the Sewage Treatment Plants into water recipient and soil.

In regard to the final two products, i.e., NanoCotz™ Eco-Clean produced by Inspiraz and Nano Plastics Coating produced by Percenta AG both of them are liquid sealants used to provide a protective coating to surfaces and plastic, respectively. Hence these two products fall into the category of products that has nanoparticles suspended in liquids, which result in a red-color code for professional end-users and consumers. The environmental exposure potential is also categorized as high especially during the initial application of the product.

Development of eight NanoRiskCat human hazard evaluation

It goes without saying that one needs to know the identity of the nanomaterial used in the product in order to answer the various questions and go through the various steps of NanoRiskCat Human Hazard Evaluation. Percenta AG that produces Nano Plastics Coating does not mention which kind of nanomaterial is used in the product and hence the answer to all the questions would have to be "No data" by default.

The first step in the Human Hazard Evaluation is to determine whether the nanomaterial fulfill the HARN paradigm? Besides for the product that uses carbon nanotubes, none of the producers mention the shape and dimensions of the nanomaterial used in their product. Carbon nanotubes generally fulfill HARN as they have a high surface area and a length to diameter aspect ratio greater than 10 to 1. Furthermore, if the CNT is a true nanomaterial it will have a considerable fraction of tubes with diameters below 100 nm and they are therefore thin enough to pass ciliated airways. The length is unknown, but as a worst case, we assume that it is long enough to initiate the onset of, e.g., frustrated phagocytosis and other inflammatory pathways; and finally, carbon nanotubes are normally considered biopersistent (Tran et al. 2008, Stone et al. 2010, NIOSH 2011a, b). Hence the color-code that best reflects the human hazard profile of carbon nanotubes is red based evidence of HARN.

The shape of the nanosilver particles used in NANOVER^{TM} Cleansing Soap are not reported, but nanosilver is normally commercialized as powder, flakes, grains, etc. (Mikkelsen et al. 2011), which do not fulfill the HARN requirements of having a diameter aspect ratio greater than 10 to 1. Bulk silver furthermore has not been classified according to CLP and either has nanosilver specifically been reported to be acute toxic (Stone et al. 2010; Mikkelsen et al. 2011). The key question in regard to the human health hazard evaluation of nanosilver is whether it fulfils question 5, i.e., are there indications that the *nanomaterial* causes genotoxic, mutagenic, carcinogenic, respiratory, cardiovascular, neurotoxic, or reproductive effects in humans and/or laboratory animals or has organ-specific accumulation been documented? Here the answer is yes for a number of reasons.

A number of in vitro studies have found that nanosilver is genotoxic and mutagenic to human lung and liver cells (AshaRani et al. 2009; Cha et al. 2008; Grigg et al. 2009; Nymark et al. 2012). A specific study on liver cell toxicity using a panel of different nanoparticles also revealed the 8–47-nm size OECD NM300K Ag nanoparticles to be inflammogenic and the most cytotoxic of all ten test materials with LC50 between 1.25 and 5 μg/cm C3A hepatocyte cell layer (maximum dose = 80 μg/cm^2), depending on methodology (Kermanizadeh et al. 2012). Because of the observed in vitro genotoxic effects of Ag nanoparticles carcinogenesis cannot be ruled out, but is not yet conclusive either due to uncertainties in test methods as discussed above.

In addition to the organ-specific in vitro tests, a number of studies have associated nanosilver with respiratory tract toxicity: For instance, investigations by Sung, et al. (2008, 2009) showed that inhalation of nanosilver 6 h/day for 5 days at concentrations of up to 3×10^6 particles/cm^3 cause decrease of lung function, e.g., tidal volume, volume of air inhaled, and peak inflammatory flow. A later inhalation study of 3.3 mg/m^3 ca. 5 nm nanosilver of 4-h exposure repeated 10 consecutive days only resulted in minimal pulmonary inflammation and cytotoxicity (Stebounova et al. 2011). Lee et al. (2008) studied nanosilver (size 13–15 nm) effect on the nasal septum respiratory mucosa of rats after exposure of 28 days and found that nanosilver affected the mucosa in rats exposed to the middle and high concentration of nanosilver. Lee et al. (2008) also demonstrated that inhalation of nanosilver for a period of 14 days changed specific brain gene expressions in mice and caused neuron disorders and neurodegenerative disease among other. With regard to reproductive damage Bar-Ilan et al. (2009) exposed zebra fish to nanosilver (3, 10, 50, and 100 nm) with a concentration at 100 or 250 μM from 4 to 120 h post-fertilization and the study showed almost 100 per cent mortality after 120 h. Furthermore, embryonic morphological malformation was observed. In a similar study on early embryonic development by Lee et al. (2007), it was observed that nanosilver accumulate in the chorion pore canals and a restricted diffusion was observed in the inner mass of the embryos. Finally, accumulation of nanosilver has been observed to be primarily accumulated in the lungs and liver, but also in the olfactory bulb, brain, and kidneys (Kim et al. 2008; Sung et al. 2009).

For dermal exposure, experimental studies have shown that low concentrations of nanosilver can pass

the skin barrier after 24-h exposure in both healthy (<2.23 ng/cm^2) and damaged skin (<11.6 ng/cm^2) (Larese et al. 2009). Samberg et al. (2010) studied the 14 day skin toxicity to eight different nanosilver (unwashed and washed uncoated 20, 50, and 80 nm nanoparticles) and carbon-coated (25- and 35-nm nanoparticles). The authors observed intracellular accumulation, focal inflammation, specifically intracellular and intercellular epidermal edema, after 14 days. Some of the effects appear to be caused by the residual contaminants in the nanosilver solutions. The authors conclude that translocation of nanosilver into cells and the body through damaged or abraded skin is important to consider. Accumulation and degradation within the cell may create reactive oxygen species that could alter cell function and cause DNA-damage (Arora et al. 2008).

Based on the literature analysis above we conclude that nanosilver should be designated a red color code that best reflects the human hazard profile. In vivo and in vitro tests show a range of potential hazards, including respiratory and genotoxic effects after inhalation. Dermal toxicity after long-term exposure seems likely. In addition, nanosilver (or dissolved Ag) have a tendency to translocate and accumulate in cells and/or inner organs. Observed genotoxicity may lead to carcinogenesis, but further investigations are necessary to confirm this. Only few studies have been carried out concerning neurotoxicity, but it is possible that problems can occur. No data on cardiovascular toxicity was found.

As in the case of nanosilver the categorization of TiO_2, ZnO, and C_{60} in regard to the human hazard evaluation comes down to whether there are indications that the nanomaterial causes genotoxic, mutagenic, carcinogenic, respiratory, cardiovascular neurotoxic, or reproductive effects in humans and/or laboratory animals or whether organ-specific accumulation has been documented?

As observed for nanoAg, we find that the red is the color code that best reflects the human hazard profile of nanoTiO_2, nanoZnO, and nanoSiO_2:

NanoTiO_2 has been intensively studied and is widely reported to cause various respiratory damage (Ferin et al. 1992; Renwick et al. 2004; Chen et al. 2006, reviewed by Stone et al. 2010), including persistent inflammation (Roursgaard et al. 2011) and allergic sensitation (Larsen et al. 2010). Other analysis also showed that some TiO_2 may cause DNA-damage in lung cells and BAL fluids and that the presence of inorganic and organic coatings on TiO_2 cause unpredictable airway toxicity (e.g., Rossi et al. 2010; Saber et al. 2012b). TiO_2 has also been associated with carcinogenicity (Heinrich et al. 1995; NIOSH 2011a, b) and IARC has concluded bulk TiO_2 to be a possible carcinogen 2B in the airways (IARC 2010). Studies suggest that inhaled TiO_2 also may cause deleterious cardiovascular (Helfenstein et al. 2008; Peters et al. 2004; Halappanavar et al. 2011), neurotoxic (Long et al. 2006, 2007; Wang et al. 2008) and reproductive effects (Komatsu et al. 2008; Hougaard et al. 2010).

For nanoZnO, Dufour et al. (2006) and Karlsson et al. (2008) has reported genotoxic and mutagenic effects, whereas Sayes et al. (2007) and Gojova et al. (2007) have associated nanoZnO with respiratory tract toxicity and cardiovascular toxicity, respectively.

For nanoSiO_2 a number of studies have reported observing genotoxic alterations, but there are conflicting studies (Mikkelsen et al. 2011). A number of studies have associated SiO_2 with respiratory toxicity. For instance Warheit et al. (1991) exposed CD rats (nose-only) for 2 or 4 weeks at concentrations of 0, 10, 50, and 150 mg/m^3 dried SiO_2 and results showed that exposures to 150 mg/m^3 for 2 or 4 weeks produced pulmonary inflammation along with increases in BAL protein, LDH, and alkaline phosphatase values and reduced macrophage phagocytosis (Stone et al. 2010). Chen et al. (2008) investigated age-related differences in cardiovascular responses to SiO_2 nanoparticles in a study with young, adult, and old rats exposed to air containing aerosol of manufactured SiO_2 nanoparticles for 4 weeks. Chen et al. (2008) found that inhalation of SiO_2 nanoparticles caused cardiovascular alterations in old rats, and less change in young and adult rats, including pulmonary inflammation, myocardial ischemic damage, atrio-ventricular blockage, and increase in fibrinogen concentration and blood viscosity (Stone et al. 2010). We conclude that the color-code that best reflects the human hazard profile of silicon and silicon dioxide is red based on in vivo evidence indicating two nanospecific hazards, namely respiratory, and cardiovascular effects.

The evidence related to C_{60} is less straightforward. C_{60} does not fulfill the HARN—paradigm; C_{60} has not been found to be acute toxic and as no bulk form of C_{60} exists, discussion about CLP classification does not make sense (Stone et al. 2010). Mutagenic effect have been observed, when exposure occurred in the

presence of visible light, due to the production of ROS, which interact with DNA to elicit damage whereas the evidence of genotoxicity of C_{60} is contradictory and therefore difficult to interpret from the studies conducted so far (Stone et al. 2010). In regard to respiratory damage an increase in the percentages/numbers of Bronchoalveolar lavage (BAL)-recovered neutrophils (i.e., white blood cells) after intratracheally instillation has been reported and so has a reduction of the viability of bovine alveolar macrophages (Sayes et al. 2007; Nielsen et al. 2008; Stone et al. 2010). Based on studies found only to be partially relevant for C_{60} data of reproductive damage collectively illustrate the potential toxicity of fullerene particles in mammalian ovary cells (Tsuchiya et al. 1996; Han and Karim 2009). Though indications of accumulation of fullerenes in organs have been described, the very reports on this end-point rather call for the answer "maybe" than the answer "yes". Overall, we find that the color code that best reflects the human hazard profile of C_{60} is yellow, i.e., "Maybe" rather than "Yes" at this point in time.

A similar kind of reasoning applies to nanoAu. NanoAu might accumulate in tissue and/or organs as De Jong et al. (2008) and Sonavane et al. (2008) have reported observing 10 nm gold nanoparticles in in the blood, spleen, liver, testis, lung, and brain in the blood, spleen, liver, testis, lung, and brain of rats 24 h after injection. Distribution in the body of rat was observed to be size dependent. It has been argued that the ability of gold nanoparticles to bind to DNA is of concern, due to the potential cytotoxic or genotoxic consequences (Johnston et al. 2010). Based on the above, we find that yellow is the color code that best reflects the human hazard profile of nanoAu.

Development of eight NanoRiskCat environmental hazard evaluation

Of the eight nanomaterials evaluated here, nanoZnO is the only material that has a bulk form that has been classified as Acute 1 or Chronic 1 or Chronic 2. Following the road-map for assigning an environmental hazard color code nanoZnO would get the color code of "red".

Silver and TiO_2 is not classified as CLP Acute 1 or Chronic 1 or Chronic 2 (Annex VI of Regulation (EC) No. 1272/2008 (CLP)). However, both nanosilver and nanoTiO_2 have been reported to be hazardous to environmental species, i.e. LC50 or EC50 < 10 mg/l. With regard to nanosilver Griffitt et al. (2008) found LC50-values of 0.04 mg/l for Daphnia pulex and 7.2 mg/l for zebrafish when testing silver nanoparticles. Zhao and Wang (2011) have established that the toxicity of silver nanoparticles is highly dependent on the surface coating and the size of the nanoparticles. The 48-h LC50 toward *Daphnia magna* varied from 28.7 to 1.1 μg/l depending on the coating of the silver nanoparticles. Hence, the environmental hazard profile of nanoAg is red.

For TiO_2, Zhu et al. (2010) reported a LC50 after 72 hours of 2.02 mgl^{-1} for nano-TiO_2 on the crustacean *D. magna* following the U.S. Environmental Protection Agency standard protocol. Hence nano-TiO_2 has been reported to be hazardous to environmental species, i.e., LC50 or EC $50 < 100$ mg/l and this indicator is fulfilled which leads to the color code of red.

C_{60} and carbon nanotubes do not have meaningful bulk parent materials and hence the answer to the question of whether to the bulk form of the materials has been classified as CLP Acute 1 or Chronic 1 or Chronic 2 does not really make sense and hence would have to be no by default. Similar to nanoAg, C_{60} has been observed to be hazardous to environmental species, i.e., LC50 or EC50 < 10 mg/l, which leads to the color code of red.

According to Stone et al. (2010) "The information available so far leads to the conclusion that non-functionalised C_{60} is toxic for aquatic organisms. A study with fish observed sub-lethal effects on growth at 0.04 mg l^{-1}". In the short-term studies with crustaceans lethal concentrations were 7.9 mg l^{-1} (LC50) for *D. magna* exposed to sonicated C_{60} and over 22.5 mg l^{-1} for copepod species exposed to stirred C_{60}. Long-term exposure of *D. magna* to 2.5 mg l^{-1} C_{60} revealed in a delay of moulting and a significant reduction in offspring. However, the effect on reproduction could have been caused by mortality which occurred from day 5 onwards. A $NOEC_{Daphnia}$ (long-term) should be <2.5 mg l^{-1} C60 (Stone et al. 2010).

As with C_{60}, nanoSiO_2 has been reported to be hazardous to environmental species, i.e., LC50 or $EC_{50} < 10$ mg/l. Adams et al. (2006) found that SiO_2 concentrations of 10 mg/l caused 70 % mortality. For algae a EC10 after 72 hours were found to be 10.9 ± 4.4 and 15.0 ± 4.3 mg/l for 12.5 and 27 nm SiO_2 nanoparticles, respectively (van Hoecke et al. 2008).

To the best of our knowledge MWCNT have not been reported to be hazardous to environmental species, i.e., LC50 or EC50 < 10 mg/l. See Jackson et al. (2013) for a substantial review of the literature. Following U.S. Environmental Protection Agency (2002) standard protocol Kennedy et al. (2008a, b) reported deriving an LC50 after 48 hours of 50.9 (38.4–67.6) mgl^{-1} on the crustacean *Ceriodaphnia dubia* and hence MWCNT has been reported to be hazardous to environmental species, i.e., LC50 or EC $50 < 100$ mg/l and this indicator is fulfilled and hence an evaluation of the persistency of nanomaterial is required. Although no OECD 301 test have been identified on MWCNT, carbon nanotubes are often said to be some of the least biodegradable man-made materials known and hence have a half-life far greater than 40 days (RCEP 2008; Hansen et al. 2012). Hence, this indicator is fulfilled leading to the color code of "red".

In regard to nanoAu, Li et al. (2010) have reported LC50-values ranging from 65 to 75 mg/l toward *D. magna* which is well below 100 mg/l. Furthermore, the $T_{1/2} > 40$ days for gold. According to Stone et al. (2010): "By definition metal nanoparticles are not degradable. However, changes in the metal speciation can occur depending on redox conditions, salt content etc. These changes in speciation are as complex as they are for conventional metal forms and no general conclusion can be made in this regard."

Final NanoRiskCat profiles of eight different nanoproducts

Once the use sentence, the human health hazard profile as well as the environmental effects profile has been developed by the user of the NanoRiskCat framework, the final NanoRiskCat profile can be developed (see Table 5).

Discussion

Interpretation of the NanoRiskCat profiles

In its simplest form the final outcome of using NanoRiskCat for a nanomaterial in a given application will be communicated in the form of a short title describing the use of the nanomaterial and five color-coded dots (e.g., •••|••). The red, yellow, and green colored dots, respectively, indicate high, medium and low potential of exposure or effect whereas the gray indicates that the data available is too limited to assess the possibility for exposure or effect.

Given the total number of available exposure profile combinations, it is somewhat surprising by the first look at Table 5 that six of the eight products have the same exposure profile and become red in regard to the professional end-users, consumers and the environment. The fact that the exposure evaluation concludes that the exposure potential is high was to be expected as many of the products are to be applied directly on the skin. Hence that there products have a red exposure category is hardly surprising. The exposure for the professional end-users and consumer are very similar, but one could easily imagine them being different for products that require the use of personal protective equipment. Although the way by which the exposure potential is determined in NRC is simplistic (e.g., a direct conclusion is made that nanoparticles suspended in liquids or airborne nanoparticles are equal to high exposure potential), this is in itself not a limitation in NanoRiskCat. It is important to note that identification of high exposure potential does not consider the exposure level and also includes the category, intended exposure. As more information about, e.g., form and concentration level of nanoparticles in various products becomes publically available, we expect that the exposure profile will be more refined and further developed.

Another interesting finding looking at Table 5 is that all the materials have or get a red environmental hazard profile, which could indicate that the approach suggested in NanoRiskCat is overly precautionary. However, we would argue that this is not the case as one would see by reading the environmental effect sentences associated with each material. From these it is evident that the reason why the materials get a red color code varies and hence there is not one single determinant that makes all materials go "red". For instance for nanoZnO it is due to properties of the bulk form of the material, whereas it for TiO_2 and SiO_2 is due to acute toxicity of the nanoforms of the material and finally, for carbon nanotubes and gold it is due to a combination of toxicity and persistency.

As in the case of the environmental profile, where there seems to be a tendency for nanomaterials used in the various products to get a red human hazard color code, it is important to note that this is due to various different concerns about a combination of effects.

Table 5 NanoRiskCat profiles for the eight different nanoproducts

	Use sentence	Exposure			Effect		Hazard sentences	
		Professional end-users	Consumers	Environment	Human health	Environmental effects	Health hazard sentence	Environmental effect sentence
1.	Nanosilver used in NANOVER™ cleansing soap						HH 7b and 8b. Based on in vivo and lin vitro evidence of a combination of two or more of the following, i.e., one of the following genotox/ mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation	EE 2. Based on nanospecific LC50 or EC50 < 10 mg/l
2.	C60 used in Bardahl XTC C60 5W40 synthetic special oil						HH 7b. Based on in vivo evidence of a combination of two or more of the following, i.e., one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation	EE 2. Based on nanospecific LC50 or EC50 < 10 mg/l
3.	Carbon nanotubes used to stiffen Babolat® NS™ Tour Tennis Racket						HH 1. Based on evidence of HARN	EE 3. Based on possible or confirmative evidence of nanospecific L50 or EC50 < 100 mg7 l and *T*1/ 2 > 40 days
4.	TiO_2 used in BaByliss Pro stylist tooks nanotitanium satin straightener						HH 8b. Based on in vitro evidence of a combination of two or more of the following, i.e., one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation	EE 2. Based on nanospecific LC50 or EC50 < 10 mg/l
5.	25-nm zinc oxide nanoparticles used in UVa and UVb reflecting solar Rx SPF 30 + nanozinc oxide sunblock						HH 8b. Based on in vitro evidence of a combination of two or more of the following, i.e., one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation	EE 1. Based on bulk CLP classification of Acute 1 or Chronic 1 or Chronic 2

Table 5 continued

	Use sentence	Exposure			Effect		Hazard sentences	
		Professional end-users	Consumers	Environment	Human health	Environmental effects	Health hazard sentence	Environmental effect sentence
6.	NanoCotz™ Eco-clean protective silicon dioxide coating						HH 7b. Based on in vivo evidence of a combination of two or more of the following, i.e., one of the following genotox/mutagenicity, respiratory effect, cardio-vascular effect, acute neurotoxic effect, reproductive damage, carcinogenicity, organ accumulation	EE 2. Based on nanospecific LC50 or EC50 < 10 mg/l
7.	Gold used in chantecaille nanogold energizing cream						HH 13. Based on in vivo evidence indicating at least one hazard from testing of the nanomaterial	EE 3. Based on possible or confirmative evidence of nanospecific L50 or EC50 < 100 mg/l and *T*1/2 > 40 d
8.	Unknown nanomaterial used in percenta AG nanosynthetic material sealant						HH 20. Based on the identity of the nanomaterial not being disclosed or available, which hampers any human hazard evaluation	EE 13. Based on the identity of the nanomaterial not being disclosed or available, which hampers any environmental hazard evaluation

Pros and cons of NanoRiskCat

When interpreting the NanoRiskCat color codes, it is important to be aware of the scope of NanoRiskCat as well as the strength and weaknesses of the proposed tool. The scope of NanoRiskCat is focused on evaluating the nanomaterial as an ingredient as it occurs in a given product considering the physical conditions and immediate availability of the nanomaterial. Hence, it could a weakness of NanoRiskCat that it does not also include an evaluation of the amount of nanomaterial in the product as well as exposure and effects from the other constituents and impurities in the product. Thus, NanoRiskCat is directed toward the generic use descriptors and scenarios, which are also apparent in the product categories used in the European chemical legislation, REACH (Regulation (EC) No. 1907/2006).

Many of the cut-off values used primarily in the environmental hazard evaluation are based on dose by mass, which represent a significant weakness of NanoRiskCat as that mass is probably not always the best metric to describe toxicity for all nanomaterials (Stone et al. 2010). Which dose metrics is the best to use in nano(eco)toxicology is an ongoing discussion. When it comes to assigning a color code to the human hazards associated with the nanoform of a given material, another weakness is that this process is based primarily on scientific expert judgment and a holistic assessment of the evidence of mutagenicity, carcinogenicity, respiratory toxicity, etc. Therefore, the human hazard color code assigned to the nanomaterial can vary as interpretation of the scientific literature can vary from expert to expert. It is not possible to provide clear-cut guidance and rules at this point in time for how to complete a holistic evaluation of the human and environmental hazards associated with the nanoform of a given material. Some might argue that this is something to strive and wish for, whereas we would argue that rigid rules would put a significant straitjacket on the emerging and exploratory field of nano(eco)toxicology and our ability to make decisions based on the newest available science.

NanoRiskCat can primarily be used to understand and categorize what is known about the hazard and exposure potential of using a given nanomaterial in a given application. By following the sketched format provided in NanoRiskCat one is able to sort, systematize and structure human and environmental hazard information on nanomaterials into an easily understandable and communicable format. The final outcome of NanoRiskCat (the short title of use scenario, the color coding and standard sentences) will make it clear whether it is the professional end-users, consumers and/or the environment that is primarily exposed and whether the nanomaterial in the product is prone to have high, medium, or low human and environmental effects. NanoRiskCat may also inform users of what kind of information is currently not available. For instance, it might be an element of concern if there is a high indication of environmental exposure, but not data available on the environmental hazards of the nanomaterial.

Another significant strength of NanoRiskCat is that it can be used even in cases where lack of data is prominent and hampers the completion of traditional risk assessment procedures. Another advantage is that the results of NanoRiskCat can be easily communicated with other interested parties. Besides being helpful for users to sort out information and structure and communicate their knowledge, NanoRiskCat can furthermore be used to do comparative analysis of two or more nanomaterials for the same application. Assuming, for instance, that the exposure profiles are the same for the two materials (i.e., ●●●), a comparative analysis of one or more alternatives would be narrowed down to an interpretation of the hazard profile of the two materials. To make a final conclusion about one being "more safe" than the other, it may be, necessary to take account of the respective concentrations of the nanomaterial in the products, the hazardous properties and the concentration of the other constituents in the products and whether there are any differences in the handling and the exposure potential between the products.

Stakeholder-dependent uses of NanoRiskCat

Decisions that could come out of using NanoRiskCat are stakeholder dependent as the tool in itself does not lead directly to a decision. Instead, it provides a more informed basis for decision-making by defining a number of concrete criteria that assist in determining the hazard and exposure potential for professional users, consumers, and the environment hence depending on the users purpose the use of NanoRiskCat may vary.

Companies can use NanoRiskCat to communicate their knowledge about the exposure and effects of the

nanomaterial they use by filling out the NanoRiskCat template and by making it available to interested parties. They could assess the need to develop guidance for safe uses that, e.g., limit exposures and/or work systematically with designing safer applications of nanomaterials. Furthermore, companies/designers could use NanoRiskCat to choose safer alternatives/applications of nanomaterials in their products. In the initial R & D process, nanomaterial researchers and developers can use NanoRiskCat to screen their materials for adverse effects and use this information to develop nanomaterials that are "safe by design", whereas producers can use NanoRiskCat to communicate what they know about the nanospecific risks of their material.

Down-stream users (e.g., consumers) can use NanoRiskCat to make a preliminary assessment of a range of nanomaterials as a means to select the seemingly most benign material. For instance, for the same use of two different nanomaterials, the exposure profile would theoretically be the same for any two nanomaterials (i.e., •••). A comparative analysis of the hazard profiles of the two materials would suggest which one it is preferable or"more safe" to use over the other, for instance, if the human and environmental hazard evaluation is"red" vs."green" and"red" vs."gray" for the two materials (•• vs. ••).

Furthermore, independent parties such as academics and non-governmental organizations can use the tools to learn more about what companies know about exposure and effect of their nanomaterials and they can use NanoRiskCat to do their own evaluation and engage in an informed dialogue about nanorisks.

Finally, regulators can use the criteria to evaluate and prioritize research efforts as well as to trigger regulatory actions. Besides using NanoRiskCat as a screening tool to flag nanomaterial use of concern and hence subject for further investigation, regulators could use NanoRiskCat to set default guidance for when regulatory measures are to be implemented, e.g., the need to consider implementation of precautionary measures that could be triggered by default if the color code of a given nanomaterial application is all red, gray, or if there are—indications of high levels of environmental exposure and environmental hazards. Regulators could also decide to develop guidance on controlled uses. For instance, requirements could be made for the use of specific personal protection equipment if there is a high possibility of exposure to professional end-users. Finally, regulators could use NanoRiskCat to set research prioritizes for instance if there is an indication of high level of exposure, but a lot of "maybes" or unknowns in regard to human and environmental hazards.

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